SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

September 10, 2002

Gaithersburg Holiday Inn
Gaithersburg, MD

Circulatory System Devices Advisory Panel Meeting
September 10, 2002

Attendees

Chairperson
Cynthia M. Tracy, M.D.
Georgetown University Hospital

Executive Secretary
Elisa Harvey, DVM, Ph.D.
Food and Drug Administration

Geretta Wood
Food and Drug Administration

Voting Members
Salim Aziz, M.D.
University of Colorado

Warren K. Laskey, M.D.
Cardiologist

Consultants
Kent R. Bailey, Ph.D.
Mayo Clinic

Kyra J. Becker, M.D.
University of Washington School of Medicine

Blase A. Carbello, M.D.
Houston VA Medical Center

Anthony Comerota, M.D.
Temple University

Ronald M. Lazar, Ph.D.
New York Neurological Institute

John R. Marler, M.D.
National Institutes of Health

Michael J. Pentecost, M.D.
Georgetown University Medical Center

Ileana Piña, M.D.
University Hospitals of Cleveland

George W. Vetrovec, M.D.
Medical College of Virginia

Christopher J. White, M.D.
Ochsner Clinic

Justin A. Zivin, M.D., Ph.D.
University of California San Diego

Consumer Representative
Robert A. Dacey

Industry Representative
Michael C. Morton
Sorin-COBE CV, Inc.

Food and Drug Administration
Bram Zuckerman, M.D.
Paul L. Chandeysson, M.D.
Doyle Gantt

CALL TO ORDER

Panel Chair Cynthia Tracy called the meeting to order at 8:07 a.m. She welcomed the participants and stated that the purpose of the meeting was to discuss and make recommendations on a PMA for the use of the CardioSEAL STARFlex Septal Occlusion System for percutaneous closure for patent foramen ovale (PFO) in high-risk patients.

Executive Secretary Elisa Harvey, DVM, Ph.D., read the conflict of interest statement. George W. Vetrovic, M.D., and Kyra J. Becker, M.D., reported interests in firms at issue in matters not related to the day's agenda; the Agency had determined that they could participate fully in the panel's deliberations. Dr. Tracy then asked the members to introduce themselves.

Executive Secretary Harvey stated that panel consultants Kent R. Bailey, Ph.D., Kyra J. Becker, M.D., Anthony Comerota, M.D., Ronald M. Lazar, Ph.D., John R. Marler, M.D., Michael J. Pentecost, M.D., George W. Vetrovec, M.D., and Christopher J. White, M.D., had been granted temporary voting status for the duration of the meeting. In addition, Blase A. Carbello, M.D., Ileana L. Piña, M.D., consultants to the Cardiovascular and Renal Drugs Advisory Committee of FDA's Center for Drug Evaluation and Research (CDER), Justin A. Zivin, M.D., Ph.D., a member of CDER's Peripheral and Central Nervous System Drugs Advisory Committee, had been appointed as voting members for the duration of the meeting.

OPEN PUBLIC HEARING

No comments were made.

SPONSOR PRESENTATION

John Ahern, chairman of the board, president, and CEO of NMT Medical, provided background information on the company. Mr. Ahern summarized the regulatory history of the

device and noted that more than 150 institutions had received approval for humanitarian device exemption (HDE) use of the device. He emphasized that the sponsor is only seeking approval to expand the current device indication.

Michael J. Landzberg, M.D., director, Boston Adult Congenital Heart Group, Brigham and Women's and Children's Hospitals, showed an animated slide presentation of the deployment of the device. The device has a self-centering mechanism for maximum coverage of the opening. Dr. Landzberg noted that that the tools required those are used in many standard cardiac procedures.

Carol Ryan, vice president for research and development, NMT Medical, listed the design characteristics of the device. The only difference between the STARFlex and the predecessor cardioSEAL device is the addition of a nitinol centering spring.

Kathy J. Jenkins, M.D., MPH, associate in cardiology, Children's Hospital, Boston, gave an overview of the clinical trial. The study is a prospective, multicenter trial that began enrollment in May 1996. It includes patients with PFO as well as other types of defects. The study has no control group. Dr. Jenkins described the selection criteria, enrollment process, and the safety and efficacy criteria. The pivotal cohort includes 49 patients. All patients had had prior neurological events; most were between ages 20 and 50 at the time they received the device.

Implantation of the STARFlex device achieved complete PFO closure in 94 percent of patients, which is greater than the predecessor devices. PFO closure resulted in significant improvement in cutaneous oxygen saturation in patients with right-to-left shunting and cyanosis. Incidence of stroke during follow up was no different than what would be expected for first or recurrent strokes in the general population, matched for age and gender. Adverse events related to the procedure were infrequent; late events were rare.

Nancy Futrell, M.D., director, Intermountain Stroke Center, Salt Lake City, provided epidemiologic information on stroke. She listed strengths of the study and made recommendations for ensuring appropriate clinical use: Neurologists should be the primary gatekeepers for the devices; labeling should define the high-risk PFO groups; distribution should be limited to centers with formal stroke programs and interventional cardiology programs; and postmarket surveillance should be conducted. Other groups may become candidates for the device, but they should not be candidates for the therapy until the studies are done. She concluded by saying that patients are benefiting from STARFlex closure and that our understanding of the role of PFO in other patient subgroups is evolving.

FDA PRESENTATION

Donna Buckley, reviewer, Office of Device Evaluation, summarized the regulatory history of the device. FDA reviewed in vitro, biocompatibility, and in vivo animal testing; no outstanding preclinical issues remain.

John Stuhlmuller, medical officer, Interventional Cardiology Devices Branch, provided information on the clinical data sets. He noted that outcome assessment for effectiveness consisted of echocardiographic assessment and neurological events; safety was assessed through analyzing the incidence of adverse events. He then listed several study limitations: vague patient selection criteria; lack of control group; and no prespecified study endpoints, success criteria, or sample size. The study is not a well-controlled investigation.

OPEN COMMITTEE DISCUSSION

Dr. Vetrovec, lead panel reviewer, noted that the panel was being asked to evaluate the safety and efficacy of a device implanted in just 49 patients. Most patients had some defined

neurological event along with high-risk attributes that warranted device placement. The sponsor provided no clear summary of admitting diagnoses that constituted a neurological event. Four neurological events were not categorized as stroke, and it is not clear that they were the neurological event that qualified the patient for the study. The use of American Hospital Association (AHA) stroke criteria is troubling; why were other published criteria not used? Only three patients had transesophageal echocardiograms (TEEs) after surgery, but most had them before implantation.

Dr. Jenkins emphasized that the study protocol is more of a clinical effectiveness than efficacy trial. The sponsor used AHA stroke data, rather than papers and literature of cohorts of patients treated medically for stroke, because the issue of baseline patient risk versus risk attributable to PFO is not well defined. The sponsor chose "to go back to the basics of simple age and gender distributions" rather than look at the literature. Follow-up studies indicate that patients can experience strokes even after PFO closures. The decision not to use TEE during follow up was because the patients had them during the procedure; in retrospect, Dr. Jenkins said, TEEs should have been done as part of follow up.

Dr. Marler, panel reviewer, asked for clarification on criteria for entry into study, which Dr. Futrell explained as "failed medical therapy." Dr. Jenkins noted that the sponsor did not tabulate prior neurological events. Dr. Marler asked if the focus was patients at risk for recurrent cryptogenic stroke. Dr. Futrell noted that such patients would be poor candidates for medical therapy and could possibly be eligible for the study. Dr. Marler asked the sponsor representative to differentiate the pivotal study patients from those in the WORS study and asked them if they would agree that there seems to be little relationship of PFO to recurrent stroke data among patients in that study. Dr. Lanzberg responded that the patients in the pivotal study are at

higher risk than the WORS patients. Extrapolating from the WORS study has to do with attributable risk due to the foramen itself; the two groups have statistically different medical confounders.

Dr. Marler expressed frustration that the sponsor had not answered his questions to his satisfaction. He pointed out that the indications are broad and that it is unclear what groups of patients will benefit from the device. Other panel members echoed his concerns about the target population, lack of selection criteria, and lack of clear evidence that repairing PFO reduces risk for stroke in high-risk patients. It was unclear how the sponsor concluded that closing the PFO is important if the stroke mechanism is unknown in the first place. Panel members noted that about 20 percent of the population has PFOs with a right-to-left shunt. In addition, the sponsor provided no clear indications for surgical failure and no tests for determining whether closure of PFO improves patient outcomes. The sponsor demonstrated safety, but not efficacy. Panel members indicated that the study would have benefited from a control group; in response, sponsor representatives indicated that a randomized study would present ethical problems. Panel members also expressed concern over the short time frame of follow up.

Dr. Bailey stated that using reduction of embolic risk as the primary endpoint was a distortion; the endpoint should have been closure of the hole. The follow-up data on the pivotal cohort was compared with the underlying risk in the population to show that the risk had been reduced to that level. Dr. Bailey stated that it did not help the sponsor's case to show that the study did not have enough power to demonstrate the reduction. **Kimberlee Gavreau, Sc.D., associate in cardiology, Children's Hospital, Boston [by speakerphone],** clarified the sponsor's statistical analysis. The confidence limits are wide because of the small sample size. Dr. Bailey said that all the study shows is that it has no power; it says nothing about the risk

compared with the general population. Dr. Gavreau replied that the study showed that risk was no worse than that of the general population.

Kathryn Hassell, M.D., associate professor of medicine, University of Colorado Health Sciences Center, said that the target population is different somehow—they have something different about their blood; an added risk is a structural hole in the heart. Closing the PFO fixes one possible mechanism of stroke. She clarified that the cohort consists of people with shunt, those with recurrent thrombotic events, and those who have contraindications to anticoagulant therapy.

Panel members discussed various methodological issues involved in a randomized study, including study size, selection criteria, and variables to consider; they expressed concern that without a randomized controlled trial (RCT), it is difficult to determine which benefits outweigh the risks of the interventions the sponsors described. Several panel members noted that the research presented was not a trial but a study; it has no prospectively defined entry, selection, or management criteria. They also expressed concern about the device fracture rate. Dr. Jenkins noted that only two fracture-related events occurred during follow up; most fractures are clinically silent. Panel members also noted that the patient brochure is over the head of the average informed patient or parent.

In response to the panel's concerns, **Carole E. Thomas, M.D., director, Acute Stroke and Neurology Critical Care Unit, Drexel University College of Medicine, Philadelphia,** said that the device is a tool that has potential for use in young patients or those who are poor candidates for anticoagulants. Such patients often would not qualify for an RCT. **Thomas Hougen, M.D., professor and chief, Division of Pediatric Cardiology, Georgetown University Medical Center,** and member of the SDMC, said that the committee has met to

review every adverse event that the study group listed; the list is extensive and detailed. The committee assigned the level of seriousness to the adverse events.

Dr. Pentecost noted that it was not clear why 12 patients did not have contrast echocardiography. Also, more than 25 percent of the patients were over age 50; why would they all of a sudden need PFO closure? The approach does not make sense pathologically. He noted that about 60 percent of the study participants were on anticoagulants 6 months after the device was inserted, treatment that seems to indicate a lack of confidence in the device. He asked what data led to the STARFlex being created, because the product seems to be in flux. Carol Ryan provided additional information on the history of the device. The device has seen three generations in 11 years; changes were made to reduce fractures, change the alloy to one with better corrosion resistance and MRI compatibility, and address residual leaks.

FDA QUESTIONS

1a. Please discuss the use of "Procedural Success" as the primary efficacy outcome measure for assessment of clinical benefit.

The panel concurred that the endpoint was not appropriate and expressed concern that entry into the study was made on a presumptive basis.

1b. Please discuss the use of the occurrence of potential embolic neurological events after device placement as a secondary efficacy outcome measure for assessment of clinical benefit.

The panel expressed concern over entry criteria and the lack of control for anticoagulant therapy; it also was concerned that the search for neurological events may not have been as complete or thorough as one would desire. The data collection issues make it impossible to know how effective the device was; also, neurological events in different population groups were not compared.

2 a. Please discuss the use of "Serious and Moderately Serious Adverse Events" (that were definitely, probably or possibly related to the device, implantation or catheterization procedure) as the primary safety outcome measure for assessment of clinical benefit versus risk.

The panel was concerned that true safety may not be totally evaluated by procedural outcome.

2b. Please discuss whether the echocardiographic evaluation and clinical evaluation (including the definitions for occurrence of neurological events) allow adequate assessment of device-related clinical events.

The panel concurred that the answer is no; more detailed pre- and postevaluation is required.

Also, seven patients were included just for closure of the shunt—stroke was not involved. More

complete hemodynamic assessment is important.

2c. Please discuss whether adequate information has been provided to allow assessment of the risk of recurrent cryptogenic stroke versus the risk of device-related neurological events.

The panel concurred that adequate information had not been provided; more time and more events were needed.

2d. Please discuss whether adequate information has been provided to characterize the appropriate post-device placement antiplatelet regimen (duration and single versus combination therapy) or anticoagulation regimen (duration and target INR).

The panel concurred that adequate information had not been provided.

3. Please comment on the lack of a pre-specified control group, pre-specified outcome measures, and pre-specified sample size.

The panel agreed that it is difficult to analyze this device because it is not clear what it is being compared to. It took a long time to accrue the 49 patients, but a small group in a well-designed study could provide more information. Clear inclusion and exclusion criteria are needed.

4. If you believe that the data presented today are inadequate to support safety and effectiveness, please address the following questions:

4a. Please clarify if additional analyses on the current data set could be performed to provide adequate information to support safety and effectiveness.

The panel concurred that the existing data set is inadequate; in the absence of additional patients,

additional analysis of the current data set will not help.

4b. Please clarify if the collection of additional data using the current patient selection criteria and outcome measures would be adequate to support safety and effectiveness.

The panel agreed that the current selection criteria and outcome measures were inadequate.

4c. Alternatively, if you believe that a new trial is required, please address the following clinical trial design questions:

4(c)(i). Given our current understanding of the causal relationship of the presence of PFO and stroke (presumed paradoxical embolism), please discuss whether a randomized trial is necessary to evaluate safety and effectiveness. If so, Can a randomized trial be completed at this time? What is an appropriate control group?

The panel noted that a sponsor has to show comparability of its device to another treatment; it has to demonstrate some kind of benefit of the device and a lack of major adverse outcomes. A controlled study is not necessarily required, but historic controls could be appropriate. The panel suggested that an aspirin/warfarin group or a "best medical therapy" group would be appropriate comparison groups. Panel members stated that an RCT for this device could be done ethically.

Bram Zuckerman, M.D., director, Division of Cardiovascular Devices, noted that this patient population has a low event rate, and the calculated sample size is going to be large. He asked the panel how a study might demonstrate benefit with a reasonable sample size. Dr. Tracy noted that the right population was included in the sponsor's study, but high risk was not clearly defined. If a study were designed correctly, it would not take an enormous number of patients to achieve an appropriate endpoint.

4(c)(ii). Please discuss whether adequate trials can be designed with historical controls or objective performance criteria.

The panel concurred that something more than historic controls are necessary; a study can be done appropriately without enlarging the patient population too much.

4(c)(iii). Based on the type of study design proposed, please address the following issues:

1. Please characterize the appropriate patient population for study enrollment.
2. Please discuss the appropriate primary and secondary outcome measures for evaluation of effectiveness and safety. As part of this discussion, please comment on the use of clinical versus surrogate endpoints.
3. Please discuss the appropriate duration of patient follow-up.
4. Please comment on what would be a clinically relevant sample size.

5. Please discuss the criteria for a successful trial.
6. Please comment on whether adjunctive antithrombotic medication regimens should be left to the operator or prospectively outlined in the protocol.

The panel felt that questions 4ciii 1 and 2 had been covered in its discussion. Concerning questions 4(c)(iii)(3–6), the primary and secondary endpoints need to be different; looking for embolic events in more sensitive manner might be an appropriate outcome. Perhaps a CT scan or MRI could serve as a surrogate for neurological events. Two-year patient follow up would be adequate, if postmarket surveillance were conducted. Regarding clinically relevant sample size, if the study were set up so that it had comparison groups within it, it would need fewer subjects. A successful trial would be one in which it is demonstrated that the intervention results in decreased events compared with best medical therapy. The role of adjunctive antithrombotic medication needs to be outlined prospectively in the study protocol.

5. Please discuss any improvements that could be made to the training program.

The panel concurred that an established proctoring system was necessary. Experience with stents alone is not sufficient. Specific observational and preceptor training is needed for the least experienced doctors.

6a. Please comment on the INDICATIONS FOR USE section as to whether it identifies the appropriate patient populations for treatment with this device.

The panel concurred that the sponsor needs to redefine the indications.

6b. Please comment on the CONTRAINDICATIONS section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

The panel agreed that the stated contraindications are based on appropriate criteria. It is unclear whether the device is appropriate for patients who cannot take aspirin or other anticoagulants.

6c. Please comment on the WARNING/PRECAUTIONS section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

The panel concurred that the warnings section is inadequate.

6d. Please comment on the OPERATOR'S INSTRUCTIONS as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

The panel concurred that the instructions are adequate.

6e. Please comment on the remainder of the device labeling as to whether it adequately describe how the device should be used to maximize benefits and minimize adverse events.

The panel concurred that the question could not be answered because of insufficient data.

7. Based on the clinical data provided in the Panel Package, do you believe that additional follow-up data or postmarket studies are necessary to evaluate the chronic effects of the implantation of the STARFlex™ device? If so, how long should patients be followed and what endpoints and adverse events should be measured?

The panel noted that long-term follow up is not available for the STARFlex, but it is available for its predecessor; STARFlex patients need to be followed for the same time frame

OPEN PUBLIC HEARING

No comments were made.

Consumer Representative Robert Dacey noted that the patient information booklet assumed too high a level of patient literacy. He suggested preparing information for patients using research on what works and does not work.

VOTE

Executive Secretary Harvey read the voting options into the record. A motion was made and seconded that the device is not approvable. The panel voted unanimously that the device is not approvable.

In describing the reasons for their votes, panel members commented that the device is safe and effective at closing the PFO, but the sponsor did not demonstrate that it is effective at

preventing recurrent strokes. Other panel members felt that the evidence is not convincing that the device is safe or effective. Carefully specified patient entry criteria are needed.

OSB PRESENTATION

Ron Kaczmarek, medical officer, Epidemiology Branch, Division of Postmarket Surveillance, Office of Surveillance and Biometrics, CDRH, presented data on pulmonary artery (PA) rupture, a rare but often fatal complication of PA catheterization. The purpose of the study was to understand problem using the FDA's Medical Device Reporting (MDR) system and the Agency for Healthcare Research and Quality's (AHRQ's) nationwide inpatient sample.

A total of 889 adverse event reports associated with PA catheters were submitted to the MDR database in the 10 years from 1991 to 2001. Of those, 71 events of PA rupture met the following case definition: hemoptysis or blood in the endotracheal tube after catheter placement or balloon inflation, *or* PA rupture in the event description of the report, *or* PA rupture in autopsy result. Of the 71 PA rupture cases, 52 were in women, resulting in 39 deaths and 13 injuries. Women composed 87 percent of the reported deaths. More PA rupture occurred among women than among men in every age group.

Using data from AHRQ's nationwide inpatient sample (NIS), Dr. Kaczmarek looked at gender difference on right heart catheterization in the 1996 sample. Most procedures (58 percent) were performed on males; PA catheterizations were more often performed in men than women in every age group. Women, however, were at increased risk of PA rupture following catheterization.

Statistical analyses indicates that female gender may be an important risk factor for PA rupture. A high index of clinical suspicion for this complication may be lifesaving because

patient survival may depend on rapid recognition and therapy. Dr. Kaczmarek summarized the limitations of the data set and suggested directions for future research. Panel members asked several questions for clarification, which Dr. Kaczmarek answered to their satisfaction.

ADJOURNMENT

Dr. Tracy thanked the participants and adjourned the meeting at 3:12 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on September 10, 2002, and that these minutes accurately reflect what transpired.

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Elisa Harvey, DVM, Ph.D.
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Cynthia M. Tracy, M.D.
Chairperson

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